



## Clinical trial results: A Single-Blind, Randomised, Parallel-Group, Single-Centre Pharmacokinetic and pH-Monitoring Study of Esomeprazole in Infants up to 24 Months of Age

### Summary

EudraCT number	2012-001159-37
Trial protocol	Outside EU/EEA
Global end of trial date	15 February 2006

### Results information

Result version number	v1 (current)
This version publication date	01 February 2017
First version publication date	12 August 2015

### Trial information

#### Trial identification

Sponsor protocol code	SH-NEC-0001
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#### Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-

Notes:

### Sponsors

Sponsor organisation name	AstraZeneca R&D Mölndal
Sponsor organisation address	Pepparedsleden 1, Mölndal, Sweden, 43183
Public contact	AstraZeneca Clinical Trial Transparency group, AstraZeneca R&D, ClinicalTrialTransparency@astrazeneca.com
Scientific contact	Per Lundborg, MD PhD, AstraZeneca R&D Mölndal, 46 317761000,

Notes:

### Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	Yes
EMA paediatric investigation plan number(s)	EMA-000331-PIP01-08
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

## Results analysis stage

Analysis stage	Final
Date of interim/final analysis	15 February 2006
Is this the analysis of the primary completion data?	Yes
Primary completion date	15 February 2006
Global end of trial reached?	Yes
Global end of trial date	15 February 2006
Was the trial ended prematurely?	No

Notes:

## General information about the trial

Main objective of the trial:

To assess the pharmacokinetics of esomeprazole and its efficacy in controlling intragastric pH in infants.

Protection of trial subjects:

The study was performed in accordance with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with ICH/Good Clinical Practice and applicable regulatory requirements and the AstraZeneca policy on Bioethics. Considerations were taken to the ICH guideline "Clinical investigation of medicinal products in the paediatric population" when developing the CSP. The study was approved by the Independent Research Ethics Committee (IEC) of the Women's and Children's Hospital, 72 King William Road, North Adelaide, South Australia 5006

Since all subjects in this study were infants aged 24 months or younger, informed consent could not be obtained from the subjects themselves. Therefore, the principal investigator ensured that the parent/guardian was given full and adequate oral and written information about the nature, purpose, possible risk and benefit of the study before enrolment. The parent/guardian was also notified that his/her child's participation in the study, as well the identity, was to be treated confidentially and that he/she was free to withdraw the child from participation in the study at any time. The parent/guardian was given time for consideration and the opportunity to ask questions. The parent's/guardian's signed informed consent was obtained before any study specific procedure was conducted.

Subjects could be withdrawn from study treatment and assessments at any time at the discretion of the investigator.

Background therapy:

The subject population comprised outpatient infants up to 24 months of age with symptoms of GERD and diagnosis confirmed by 24-hour pH-monitoring. Medication considered necessary for the subject's safety and well-being was to be given at the discretion of the investigator. Use of any pharmacological antireflux therapy within 24 hours prior to the first dose of investigational product, or use of any proton pump inhibitor within 72 hours of the first dose of investigational product were exclusion criteria. Mylanta or equivalent could be used for treatment of gastrointestinal symptoms, except within +/- 1 hour of the administration of investigational product.

Evidence for comparator:

No comparator group

Actual start date of recruitment	06 June 2002
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

## Population of trial subjects

### Subjects enrolled per country

Country: Number of subjects enrolled	Australia: 50
Worldwide total number of subjects	50
EEA total number of subjects	0

Notes:

<b>Subjects enrolled per age group</b>	
In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	50
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

## Subject disposition

### Recruitment

Recruitment details:

First subject enrolled 6 June 2002

Last subject completed 23 March 2005

### Pre-assignment

Screening details:

107 subjects attended pre-entry visit <7 days before first study day. At pre-visit informed consent was obtained, routine lab, physical examination and 24-hour pH monitoring was performed. Out of these, 50 eligible subjects were randomised to 1 of the parallel treatment arms and given a subject number 2 days prior to first dose administered.

### Pre-assignment period milestones

Number of subjects started	50
Number of subjects completed	50

### Period 1

Period 1 title	Treatment period (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Single blind
Roles blinded	Carer <sup>[1]</sup>

### Arms

Are arms mutually exclusive?	Yes
<b>Arm title</b>	Esomeprazole 0.25 mg/kg

Arm description:

Esomeprazole 0.25 mg/kg

Arm type	Experimental
Investigational medicinal product name	Esomeprazole
Investigational medicinal product code	
Other name	NEXIUM
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

0.25 mg/kg orally od for 1 week

<b>Arm title</b>	Esomeprazole 1.0 mg/kg
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Arm description:

Esomeprazole 1.0 mg/kg

Arm type	Experimental
Investigational medicinal product name	Esomeprazole
Investigational medicinal product code	
Other name	NEXIUM
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

1.0 mg/kg orally od for 1 week

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Notes:

[1] - The roles blinded appear inconsistent with a simple blinded trial.

Justification: Individual NSAE occurring in > 1 subject in the trial (>5%) is included

<b>Number of subjects in period 1</b>	Esomeprazole 0.25 mg/kg	Esomeprazole 1.0 mg/kg
Started	26	24
Completed	23	22
Not completed	3	2
Consent withdrawn by subject	2	2
Adverse event, non-fatal	1	-

## Baseline characteristics

### Reporting groups

Reporting group title	Esomeprazole 0.25 mg/kg
Reporting group description: Esomeprazole 0.25 mg/kg	
Reporting group title	Esomeprazole 1.0 mg/kg
Reporting group description: Esomeprazole 1.0 mg/kg	

Reporting group values	Esomeprazole 0.25 mg/kg	Esomeprazole 1.0 mg/kg	Total
Number of subjects	26	24	50
Age Categorical			
1 month up to 24 months of age			
Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	26	24	50
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	0	0	0
From 65-84 years	0	0	0
85 years and over	0	0	0
Esomeprazole low	0	0	0
Age Continuous			
Study included infants aged 1 month up to 24 months			
Units: months			
arithmetic mean	6.9	7	
full range (min-max)	2.3 to 22.2	2.2 to 23.8	-
Gender Categorical			
Units: Subjects			
Female	9	10	19
Male	17	14	31

### Subject analysis sets

Subject analysis set title	ITT population
Subject analysis set type	Intention-to-treat
Subject analysis set description: All randomised subjects who took at least 1 dose of study medication and for whom pharmacokinetic, pharmacodynamic or symptom data post-dose are available were included in the ITT population	

Reporting group values	ITT population		
Number of subjects	50		

Age Categorical			
1 month up to 24 months of age			
Units: Subjects			
In utero	0		
Preterm newborn infants (gestational age < 37 wks)	0		
Newborns (0-27 days)	0		
Infants and toddlers (28 days-23 months)	50		
Children (2-11 years)	0		
Adolescents (12-17 years)	0		
Adults (18-64 years)	0		
From 65-84 years	0		
85 years and over	0		
Esomeprazole low			
Age Continuous			
Study included infants aged 1 month up to 24 months			
Units: months			
arithmetic mean	7		
full range (min-max)	2.2 to 23.8		
Gender Categorical			
Units: Subjects			
Female	19		
Male	31		

## End points

### End points reporting groups

Reporting group title	Esomeprazole 0.25 mg/kg
Reporting group description:	
Esomeprazole 0.25 mg/kg	
Reporting group title	Esomeprazole 1.0 mg/kg
Reporting group description:	
Esomeprazole 1.0 mg/kg	
Subject analysis set title	ITT population
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
All randomised subjects who took at least 1 dose of study medication and for whom pharmacokinetic, pharmacodynamic or symptom data post-dose are available were included in the ITT population	

### Primary: Pharmacokinetic variables AUC<sub>T</sub>

End point title	Pharmacokinetic variables AUC <sub>T</sub> <sup>[1]</sup>
End point description:	
AUC <sub>T</sub>	
End point type	Primary
End point timeframe:	
1 week (7 or 8 days)	

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: For the pharmacokinetic endpoints only descriptive statistics were used.

End point values	Esomeprazole 0.25 mg/kg	Esomeprazole 1.0 mg/kg	ITT population	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	17 <sup>[2]</sup>	18 <sup>[3]</sup>	35 <sup>[4]</sup>	
Units: µmol*h/L				
geometric mean (confidence interval 95%)	0.24 (0.12 to 0.48)	1.79 (0.9 to 3.56)	7.62 (2.85 to 20.4)	

Notes:

[2] - PK total 40 subjects, in 5 of these no PK value due to too few post-dose samples or below LLQ

[3] - PK total 40 subjects, in 5 of these no PK value due to too few post-dose samples or below LLQ

[4] - Ratios for the Geometric means (Eso 1.0 mg/kg/Eso 0.25 mg/kg) and confidence intervals presented

### Statistical analyses

No statistical analyses for this end point

### Primary: Pharmacokinetics C<sub>max</sub> steady state

End point title	Pharmacokinetics C <sub>max</sub> steady state <sup>[5]</sup>
End point description:	
End point type	Primary
End point timeframe:	
at 1 week (day 7/8)	

Notes:

[5] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: For the pharmacokinetic endpoints only descriptive statistics were used.

End point values	Esomeprazole 0.25 mg/kg	Esomeprazole 1.0 mg/kg	ITT population	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	17 <sup>[6]</sup>	17 <sup>[7]</sup>	34 <sup>[8]</sup>	
Units: µmol/L				
geometric mean (confidence interval 95%)	0.17 (0.09 to 0.31)	0.85 (0.45 to 1.6)	5.08 (2.09 to 12.35)	

Notes:

[6] - PK total 40 subjects, in 5 of these no PK value due to too few post-dose samples or below LLQ

[7] - PK total 40 subjects, in 5 of these no PK value due to too few post-dose samples or below LLQ

[8] - Ratios for the Geometric means (Eso 1.0 mg/kg/Eso 0.25 mg/kg) and confidence intervals presented

## Statistical analyses

No statistical analyses for this end point

## Primary: PharmacodynamicThe percentage of time with intragastric pH above 4 during the 24-hour period

End point title	PharmacodynamicThe percentage of time with intragastric pH above 4 during the 24-hour period
End point description:	
The percentage of time with intragastric pH above 4 during the 24-hour period	
End point type	Primary
End point timeframe:	
pre-entry visit and on Day 7/8	

End point values	Esomeprazole 0.25 mg/kg	Esomeprazole 1.0 mg/kg	ITT population	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	22 <sup>[9]</sup>	22 <sup>[10]</sup>	44 <sup>[11]</sup>	
Units: percentage of time				
geometric mean (confidence interval 95%)	47.91 (39.35 to 56.47)	69.25 (60.69 to 77.82)	21.34 (9.23 to 33.45)	

Notes:

[9] - Subjects who had intragastric pH measurement

[10] - Subjects who had intragastric pH measurement

[11] - Difference between treatment groups

## Statistical analyses

Statistical analysis title	Intragastric pH>4 after one week of treatment
Comparison groups	Esomeprazole 0.25 mg/kg v Esomeprazole 1.0 mg/kg v ITT population

Number of subjects included in analysis	88
Analysis specification	Pre-specified
Analysis type	superiority
P-value	> 0.0009
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	21.34
Confidence interval	
level	95 %
sides	2-sided
lower limit	9.23
upper limit	33.45
Variability estimate	Standard error of the mean
Dispersion value	6

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

During enrollment and randomised treatment (1 week)

Assessment type	Systematic
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### Dictionary used

Dictionary name	MedDRA
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Dictionary version	Not known
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### Reporting groups

Reporting group title	Esomeprazole 1.0 mg/kg
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Reporting group description:

Esomeprazole 1.0 mg/kg

Reporting group title	Esomeprazole 0.25 mg/kg
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Reporting group description:

Esomeprazole 0.25 mg/kg

Serious adverse events	Esomeprazole 1.0 mg/kg	Esomeprazole 0.25 mg/kg	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 24 (0.00%)	0 / 26 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Esomeprazole 1.0 mg/kg	Esomeprazole 0.25 mg/kg	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	6 / 24 (25.00%)	6 / 26 (23.08%)	
Gastrointestinal disorders			
Vomiting			
subjects affected / exposed	1 / 24 (4.17%)	1 / 26 (3.85%)	
occurrences (all)	6	6	
Psychiatric disorders			
Irritability			
subjects affected / exposed	2 / 24 (8.33%)	1 / 26 (3.85%)	
occurrences (all)	6	6	
Infections and infestations			

Nasopharyngitis subjects affected / exposed occurrences (all)	2 / 24 (8.33%) 6	1 / 26 (3.85%) 6	
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## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
10 December 2001	Addition of exclusion criteria no 2; "Current or previous evidence of liver disease and necrotising enterocolitis".
14 February 2002	information that "At least 24 of the 40 evaluable subjects should be less than 12 months of age" was added.
27 February 2002	Clarification around antacids as rescue medication
05 February 2003	The study was changed from being double-blind to become single-blind, and prolongation of recruitment time.
02 April 2003	Change of exclusion criteria no 5a; Reflux index for subjects $\leq 12$ months of age was change from $\geq 10\%$ to $\geq 5\%$
14 September 2003	The CSP was changed to also include infants 1 to 3 months of age in order to comply with an FDA request.
20 January 2004	The methods of drug administration for subjects $\geq 1$ month but $< 3$ months of age was changed (through funnel pan)
07 April 2004	The number of pharmacokinetically evaluable subjects needed in the study was changed from 40 to 30 subjects,
09 September 2004	date for last subject out was postponed until first/second quarter of 2005

Notes:

### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported